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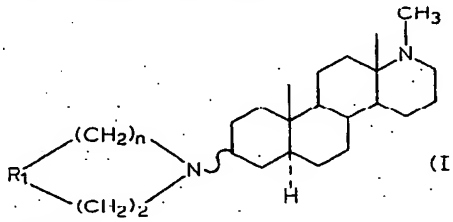
(54) **3-Amino-17a-aza-D- homoandrostane derivatives**

(57) Compounds of general formula I



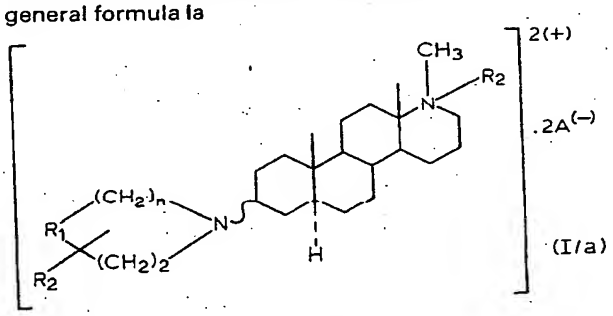
(I)

wherein

R_1 represents a methylene or N-CH_3 group;

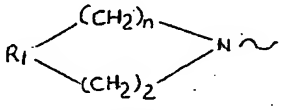
n is 1 or 2; and

the symbol indicates an α- or β-configuration and the acid addition salts thereof and the quaternary salts of general formula Ia



(Ia)

wherein R_1, n and ~ are as defined above, R_2 represents an alkyl or alkenyl group containing from 1 to 4 carbon atoms and A represents a halogen atom with the proviso that, when R_1 represents an N–CH_3 group then the R_2 group attached to the ring including R_1 is attached to the nitrogen atom of said R_1 group and when R_1 represents a methylene group then the R_2 group attached to the ring including R_1 is attached to the nitrogen atom of the group

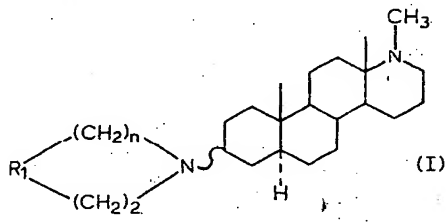


Said compounds possess interesting pharmacological properties in particular as competitive neuromuscular blocking agents.

SPECIFICATION

3-Amino-17a-aza-D- Homoandrostane Derivatives

This invention relates to new 3-amino-17a-aza-D- homoandrostane derivatives, their preparation and pharmaceutical preparations containing them. More particularly the invention relates to 3-amino-17a-aza-D-homoandrostane derivatives of the general formula



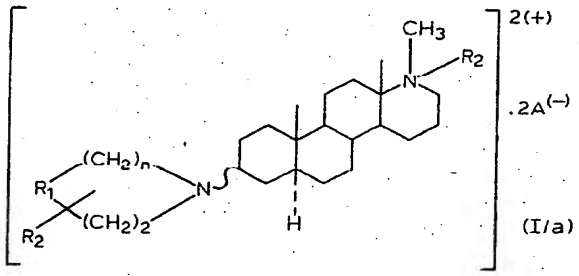
(I)

wherein

R_1 represents a methylene or an $\geq N-CH_3$ group;

n = 1 or 2; and

the symbol ~ represents an α- or β-configuration, and acid addition salts and quaternary salts thereof. The quaternary salts of the compounds having the general formula I are encompassed by the general formula I/a



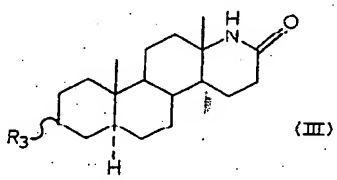
(I/a)

wherein R_1, n and the symbol ~ have the same meaning as defined above, and

R_2 represents an alkyl or alkenyl group having from 1 to 4 carbon atoms each, provided that is R_1 represents an $\geq N-CH_3$ group, R_2 is attached to the $\geq N-CH_3$ group; and

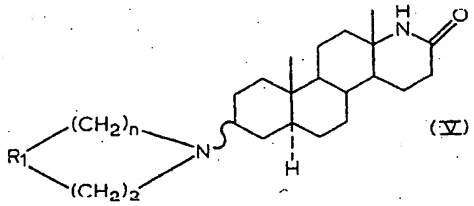
A represents a halogen atom.

Compounds of the general formulae I and I/a and the intermediates of their synthesis characterized by the general formulae



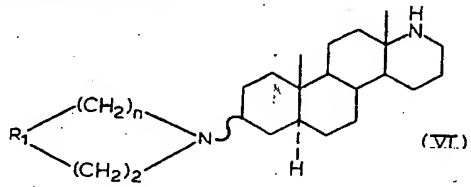
(III)

wherein R_3 is an alkene-sulphonyloxy, an aryl- or an aralkyl-sulphonyloxy group;



(V)

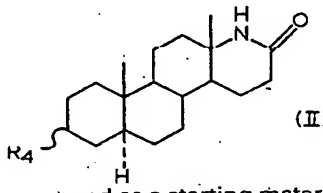
wherein the symbols are as defined above; and



(VI)

wherein the symbols are as defined above, are new compounds which have not been reported before in the literature. The structurally closest known compounds are described in the British Patent Specification No. 1,345,971. These compounds are 17-aza-pregnane derivatives and show bacterid and cholesterine level decreasing activity.

The compound of the formula



(II)

wherein R_4 is an α- or β-hydroxyl group, used as a starting material is well known and has for instance been described in Tetrahedron *21* (4), 734-57 (1965); Helv. Chim. Acta *38*, 1404 (1955).

The new compounds of the general formula I possess valuable physiological properties and their quaternary salts of the general formula I/a are excellent non-depolarising neuromuscular blocking agents having a short activity period.

Especially preferred compounds according to the invention include the following compounds of formula I/a:

3α-Pyrrolidino-17a- methyl-17a- aza -D- homo-5α- androstane dimethoiodide;

3β-Pyrrolidino-17a- methyl-17a-aza-D- homo-5α- androstane dimethoiodide and

3β-Pyrrolidino-17a- methyl-17a-aza-D- homo-5α- androstane dimethobromide;

and the most preferred compound is

3α-Pyrrolidino-17a-methyl-17a- aza-D-homo-5α- androstane dimethobromide.

It is well known that in the theraphy first of all those muscle relaxants are used which have a more favourable effect - i.e. are easy to control - and which are of non-polarising - i.e. competitive - type [Negwer (1971) 4821], such as for example pancuronium bromide. These compounds generally have a prolonged activity and as a short activity-type muscle relaxant almost exclusively thedepolarising suxamethonium is employed [Negwer (1971) 2289].

Until now there has been used no muscle relaxant preparation in the theraphy which has a short activity period and which belongs to the non-depolarising agents. The object of the present invention is to provide compounds having about the same activity period as suxamethonium but belonging to the non-polarising compounds. The new compounds are therefore easy to control during their therapeutical application.

The compounds according to the invention are competitive neuromuscular blocking agents, i.e. inhibit the transmission of the nervous stimulus to the transverse muscles. The activity of these compounds can be compensed by acetylcolinesterase inhibitors, e.g. fizostigmine. They have no influence on the blood circulation and on the endocrine activity.

The potency and the activity period of the compounds according to the invention were tested on anesthesized cats and alert dogs. On anesthesized cats the peroneal nerve was electrically stimulated and the corresponding contraction of the tibialis muscle was registered. The i.v. doses of the various test compounds which reduced the contactions to half of their original values were determined. /$ED_{50\text{-values}}$/ In the attached Table I the ED_{50}-values and the corresponding activity periods are shown, wherein term "activity period" is intended to mean the time interval between the first appearance of the effect of the test compounds and the restoration of the normal muscle contractions. For each test compound 4 doses and for each dose 6 animals were examined. As a reference compound suxamethonium was used, which is a known compound widely used as a neuromuscular blocking agent having a short activity period. It was found that the compounds according to the invention caused a neuromuscular block which had about the same length of time as the block induced by suxamethonium.

To alert dogs 6 animals for each test compound four doses causing a total muscle relaxation were administered and the time between the administration and the total muscle relaxation as well as the time between the administration and the disappearance of the activity was measured. The experimental data are set forth in the Table II. It has been found that the time of disappearance is shorter for the new compounds than for suxamethonium.

Table I

Compound	ED_{50} /mcg/kg/	Activity period/min/
3α -Pyrrolidino-17a-methyl-17a--aza-D-homo-5α-androstane-dimethobromide	100	11.2
3α -Pyrrolidino-17a-methyl-17a--aza-D-homo-5α-androstane-dimetholodide	120	12.4
3β -Pyrrolidino-17a-methyl-17a--aza-D-homo-5α-androstane-dimethobromide	125	13.0
3β -Pyrrolidino-17a-methyl-17a--aza-D-homo-5α-androstance-dimethoiodid	105	12.6
Suxamethonium	60	11.0

Table II

Compound	Dose	Time until the max. effect/sec/	Activity period /min/
3α -Pyrrolidino-17a-methyl-17a--aza-D-homo-5α-androstane-dimethobromide	100	18	8.6
3α -Pyrrolidino-17a-methyl-17a--aza-D-homo-5α-androstane-dimethoiodide	100	19	8.5
3β -Pyrrolidino-17a-methyl-17a--aza-D-homo-5α-androstane-dimethobromide	100	21	9.5
3β -Pyrrolidino-17a-methyl-17a--aza-D-homo-5α-androstane-dimethoiodide	100	17	8.8
Suxamethonium	100	16	10.3

The biologically active compounds according to the invention are used for pharmacological purposes in the form of conventional pharmaceutical compositions.

The compounds according to the invention may be formulated into pharmaceutical compositions in the conventional manner.

Thus according to a further feature of the present invention there are provided pharmaceutical compositions comprising at least one compound of formula I or I/a or a physiologically compatible acid addition salt of a compound of formula I as defined in claim 1 in association with a pharmaceutical carrier or excipient.

The pharmaceutical compositions according to the invention are first of all suitable for parenteral administration.

As pharmaceutical carriers various inert compounds are used, which do not react with the active ingredients, e.g. water. The compositions can also be sterilized.

The compositions may also contain various additives which change the osmotic pressure, e.g. salts or buffers.

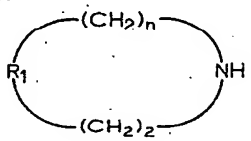
In order to prepare injection solutions the active ingredients are dissolved in a pyrogen-free physiological sodium chloride solution or in water distilled twice to give formulations having an active ingredient concent-

ration of 0.5 to 10 mg./ml. The injection solutions are then sterilized and filled into ampoulles under sterile conditions.

For the treatment of adult human patients the active ingredients are administered in a dose of 0.1 to 0.5 mg./kg body weight. They are advantageously used to facilitate short medical treatments, first of all in the surgery - incubation, treatment of fractions, sprains - and may also be employed in a shock treatment as muscle relaxants.

The compounds of the general formula I as hereinbefore defined and the acid addition salts and quaternary salts thereof - the latter being encompassed by the general formula I/a - may be prepared by the following process, which process constitutes a further feature of the present invention:–

A known compound of the general formula II, wherein R_4 is as hereinbefore defined, is reacted with an alkyl- aryl- or aralkylsulphonic acid halide to prepare a compound of the general formula III, in which R_3 is as hereinbefore defined; the compound of the general formula III obtained is then reacted with a heterocyclic amine derivative of the general formula IV



(IV)

wherein R_1 and n are as hereinbefore defined; then a compound of the general formula V obtained, wherein R_1, n and the symbol ~ are as hereinbefore defined, is reduced to give a compound of the general formula VI, wherein R_1, n and the symbol ~ are as defined above, which is methylated to afford a compound of the general formula I, wherein R_1, n and the symbol are as defined above, which is optionally converted into an acid addition salt thereof, or is optionally reacted with an alkyl or alkenyl halide to produce a corresponding quaternary salt of the general formula I/a, wherein R_1, R_2, A, n and the symbol ~ are as hereinbefore defined.

According to a preferred embodiment of the process of the invention the compounds of the general formula I are prepared as follows:–

A known compound of the general formula II [Tetrahedron *21* (4), 743-57 (1965); Helv. Chim. Acta *38*, 1404 (1955)] is reacted with a sulphonic acid halide, preferably with methanesulphonic acid chloride or *p*-toluene-sulphonic acid chloride, in a tertiary amine or in a mixture of a tertiary amine, such as pyridine and a reaction-inert solvent, preferably methylene chloride, at a temperature of below 30°C, preferably at 5 to 10°C. When the reaction terminates the mixture is poured onto water, the precipitated product is filtered off, is released from the tertiary amine by washing with a dilute acid and subsequently with water, or alternatively the product is extracted with methylene chloride to eliminate the tertiary amine. To an alkyl- or aralkylsulphonic acid derivative of formula III obtained a five- or six-membered heterocyclic amine containing one or two nitrogen atoms, preferably pyrrolidine, N-methylpiperazine piperidine is added, and the mixture obtained is kept at a temperature of below 140°C, preferably at the boiling point of the mixture, optionally in the presence of a solvent until the reaction terminates. Thereafter the excess of the heterocyclic amine and optionally the reaction-inert solvent are distilled off, the residue is triturated with water, filtered, and washed with water to eliminate the heterocyclic amine reactant; or alternatively the residue is evaporated, triturated with a suitable solvent, preferably with acetone or acetonitrile and is filtered off. If desired, the product obtained is purified by recrystallization or boiling. The compound of the general formula V prepared in this way is reduced with a complex metal hydride, preferably with lithium-aluminium hydride or sodium-bis-/2-methoxyethoxy/- lithium- aluminium- hydride, in a reaction-inert solvent, e.g. tetrahydrofurane or dioxane, preferably at the boiling point of the reaction mixture. The reaction terminates in 1-2 to 40-50 hours. Thereafter the excess of the reducing agent is decomposed in a manner known *per se*, for example with water or ethyl acetate in the presence of nitrogen, the precipitate is filtered off and is washed several times preferably with the solvent used as a reaction medium. Upon evaporation of the solvent and the wash liquor the residue is crystallized.

The compound of the general formula VI obtained is methylated as follows:–

The compound is dissolved in an excess amount of formic acid and formeldehyde and the reaction mixture is boiled for several hours. When the reaction terminates the mixture is evaporated until a syrupy residue is obtained, which is alkalized, diluted with water, filtered and is washed to neutral with water. The compound of formula I obtained is purified by crystallization from a polar solvent, for instance ether, acetone.

If desired, compounds of formula I are converted into the non-toxic physiologically compatible organic or inorganic acid addition salts thereof, by methods known *per se*. In the living organism especially the inorganic hydrogen halide acid addition salts and the organic acetates, gluconates, tartarates and alkylsulphonates show the most advantageous properties.

Compounds of the general formula I/a are prepared from the bases of the general formula I by dissolving a corresponding compound of formula I in a reaction-inert solvent, preferably acetone or in a mixture of acetone and methylene chloride and a solution of an excess amount of a corresponding alkyl or alkenyl halide, preferably methyl bromide, methyl iodide or allyl bromide in an appropirate solvent used as a reaction medium is added. The reaction is performed at room temperature or at the boiling temperature of the reaction mixture, under atmospheric pressure or in a bomb tube, under an overpressure of several atm.

When the reaction terminates the precipitated product is filtered off, and the product is isolated optionally after distilling off the solvent or solvent mixture and the excess of the quaternarizing compound, preferably by treating with ether or acetone. The above solvent may also be added directly to the reaction mixture, when the precipitated product is filtered off and, if desired, is recrystallized.

The process according to the invention is further illustrated by the following non-limiting Examples.

EXAMPLE 1

3α-Pyrrolidino-17a-methyl-17a- aza -D-homo-5α- androstane dimethobromide

2 g. (0.0055) moles) of 3α-pyrrolidino-17a- methyl-17a-aza-D- homo-5α- androstane are dissolved in a mixture of 50 ml. of dry acetone and 50 ml. of dry methylene chloride, whereupon a solution of 3.29 g. (0.034 moles) of methylbromide in 35 ml. of acetone is added to the solution. The reaction mixture is allowed to stand at room temperature for 32 hours. The progress of the reaction is monitored by thin layer chromatography. When the reaction terminates the solvent is distilled off and the precipitated crystalline product is filtered, washed thoroughly with a 1:1 mixture of methylene chloride and acetone and is crystallized from a mixture of ethanol and ether.

Yield: 2.49 g. (81.4 %) of 3α-pyrrolidino-17a- methyl-17a-aza-D- homo-5α- androstane dimethobromide
M.p.: 288 to 290°C (decomposition)
$[\alpha]^{25}_D$ = + 28.6° (c: 1% in chloroform)
NMR spectrum: 0.79 (19 CH_3) ; 1.49 (18 CH_3) ; 3.11 (3 NCH_3) ; 2.94 (17a NCH_3).

Analysis for $C_{26}H_{48}N_2Br_2$:
Calculated: C = 56.93 %, H = 8.75 %, N = 5.10 %, Br = 29.19 %;
Found: C = 56.71 %, H = 8.60 %, N = 5.00 %, Br = 28.92 %.

3α-pyrrolidino-17a-methyl-17a-aza -D- homo-5α- androstane used as a starting compound is prepared as described hereinbefore.

EXAMPLE 1A

3β-Mesyloxy-17- oxo-17a-aza-D- homo-5α- androstane

40 g. (0.131 moles) of 3β-hydroxy-17- oxo-17a-aza-D- homo-5α- androstane are dissolved in 600 ml. of dry pyridine then 20.8 g. (0.181 moles) of methanesulphonic acid chloride are added to the solution with vigorous stirring so that the temperature remains between 0° and 5°C. The resultant reaction mixture is stirred for further 3 hours at the same temperature while the progress of the reaction is monitored by thin layer chromatography. When the reaction terminates the pyridine solution is added dropwise to 4000 ml. of ice-water, the precipitated product is filtered off and washed to pyridine-free and neutral with water, a 2 % aqueous hydrochloric acid solution and again with water. The product obtained is dried at 60°C *in vacuo*.

Yield: 48 g. (95.5 %) of 3β-mesyloxy-17-oxo-17a- aza-D-homo-5α-androstane
M.p.: 167° to 168°C
$[\alpha]^{25}_D$ + = 13.9 (c = 1% in chloroform)
IR spectrum: 1170 cm^{-1}(SO_2): 1160 cm^{-1} (amide I)
NMR spectrum: 0.82 (19 CH_3) ; 1.15 (18 CH_3) ; 3.00 (3 SO_2CH), 4.60 (3α H) ; 6.70 (17a NH).

Analysis for $C_{20}H_{33}O_4NS$:
Calculated: C = 62.66 %, H = 8.61 %, N = 3.65 %;
Found: C = 62.40 %, H = 8.40 %, N = 3.50 %.

EXAMPLE 1B

3β-Tosyloxy-17-oxo- 17a-aza-D- homo-5α- androstane

130 g. (0.283 moles) of 3β-hydroxy -17- oxo-17a- aza-D- homo-5α- androstane are dissolved in 3900 ml. of dry pyridine, then 283 g. (1.44 moles) of freshly recrystallized *p*-toluene - sulphochloride are added to the solution. The reaction mixture is allowed to stand at room temperature for 24 hours, while the progress of the reaction is monitored by thin layer chromatography. When the reaction terminates the pyridine solution is added into 20 lit. of ice-water with vigorous stirring. The precipitated product is filtered off and washed to pyridine-free and neutral with a 2 % aqueous hydrochloric acid solution and water. The product obtained is dried at 60° to 70°C *in vacuo*, then boiled in 700 ml. of acetone under stirring.

Yield: 158 g. (80.7 %) of 3β-tosyloxy-17-oxo -17a-aza-D- homo-5α- androstane
M.p.: 258° to 260°C
$[\alpha]^{25}_D$ = −2.2° (c = 1 % in chloroform)
IR spectrum: 1175 cm^{-1}(SO_2); 1665 cm^{-1} (amide I)
NMR spectrum: 0.75 (19 CH_3) ; 1.12 (18 CH_3) ; 2.43 (tosylmethyl) ; 4.40 (3α H) ; 6.95 (17a NH).

Analysis for $C_{26}H_{37}O_4NS$:
Calculated: C = 67.97 %, H = 8.06 %, N = 3.05 %,
Found: C = 67.62 %, H = 7.82 %, N = 2.90 %.

EXAMPLE 1C

3α-Pyrrolidino-17- oxo-17a-aza-D- homo-5α- androstane

16 g. (0.041 moles) of 3α-mesyloxy-17-oxo -17a-aza-D- homo-5α- androstane are dissolved in 100 ml. of pyridine. The solution is refluxed for 20 hours and subsequently cooled to room temperature. The precipitated crystalline substance is filtered off and washed to pyrrolidine-free with water. The mother liquor is evaporated, the residue is triturated with water, filtered and thoroughly washed with water. The two crystalline products are combined, dried at 60° to 70°C *in vacuo*, and boiled in 60 ml. of acetonitrile with stirring.

Yield: 13.7 g. (91.6 %) of 3α-pyrrolidino-17- oxo-17a-aza-D- homo-5α-androstane
M.p.: 285° to 288°C
$[\alpha]_D^{25}$ = + 13.3 (c = 1 % in chloroform)
IR spectrum: 1660 (amide I) ; 2880 to 2500 (N-CH_3)
Analysis for $C_{23}H_{38}ON_2$:
Calculated: C = 77.09 %, H = 10.61 %, N = 7.83 %;
Found: C = 76.80 %, H = 10.50 %, N = 7.70 %.

EXAMPLE 1D
3α-Pyrrolidino- 17a-aza-D- homo-5α- androstane

10.5 g (0.029 moles) of 3α-pyrrolidino-17- oxo-17a-aza-D- homo-5α- androstane are dissolved in 205 ml. of dry dioxane, whereupon 10.5 g. of lithium-aluminium hydride are carefully added to the solution under a nitrogen flow. The reaction mixture is brought to the boil in an apparatus equipped with a $CaCl_2$-tube and a reflux condenser and is refluxed for about 30 minutes. Thereafter the reaction mixture is cooled to 10°C and the excess of lithium-aluminium hydride is decomposed with 20 ml. of water with stirring, under a vivid nitrogen flow. The precipitate consisting of lithium hydroxide and aluminium hydroxide is filtered and thoroughly washed with several portions of dioxane. The dioxane solution obtained is evaporated to dryness and the residue is purified by precipitation.

Yield: 9.1 g. (90.2 %) of 3α-pyrrolidino-17a-aza-D- homo-5α- androstane
M.p.: 84° to 85°C
$[\alpha]_D^{25}$ = + 4.6° (c = 1 % in chloroform)
NMR spectrum: 0.79 (19 CH_3) ; 1.02 (18 CH_3) ; 2.8 (17 CH_2)
Analysis for $C_{23}H_{40}N_2$:
Calculated: C = 80.23 %, H = 11.62 %, N = 8.13 %;
Found: C = 80.01 %, H = 11.50 %, N = 7.92 %.

EXAMPLE 1E
3α-Pyrrolidino-17a- methyl-17a-aza-D- homo-5α- androstane

7.1 g (0.02 moles) of 3α-pyrrolidino -17a-aza-D- homo-5α-androstane are dissolved in a mixture of 85 ml. of formic acid and 64 ml. of formaldehyde, then the mixture is refluxed for 2.5 hours. A further 64-ml. portion of formaldehyde is added to the reaction mixture and it is refluxed for further 2 hours. The reaction mixture is then evaporated to near to dryness and its pH-value is adjusted to 10 with a 5 % aqueous sodium hydroxide solution. The precipitated amorphous substance is filtered off, washed to neutral with water and dried at 50° to 60°C *in vacuo*. The product is purified by boiling with 40 ml. of ether.

Yield: 5.6 g. (75.9 %) of 3α-Pyrrolidino-17a- methyl-17a- aza-D-homo-5α- androstane
M.p.: 156° to 158°C
$[\alpha]_D^{25}$ = + 9.8° (c = 1 % of chloroform)
NMR spectrum: 0.77 (19 CH_3) ; 0.83 (18 CH_3) ; 2.21 (17a NCH_3)
Analysis for $C_{24}H_{24}N_2$:
Calculated: C = 80.44 %, H = 11.73 %, N = 7.82 %;
Found: C = 80.20 %, H = 11.52 %, N = 7.71 %.

EXAMPLE 2
3α-Pyrrolidino-17a- methyl-17a-aza-D- homo-5α- androstane dimethoiodide

2 g. (0.0055) moles of 3α-pyrrolidino-17a- methyl-17a-aza- D-homo-5α- androstane are dissolved in a mixture of 10 ml. of acetone and 15 ml. of ethanol at the boiling temperature, then 4 g. (0.028 moles) of methyl iodide are added to the boiling reaction mixture. Boiling is continued for about 60 minutes, whereupon the reaction mixture is cooled to below 10°C, the precipitated crystals are filtered off and washed with an acetone/ethanol mixture which has the above composition.

Yield: 2.8 g 79.09 %3α-pyrrolidino-17a- methyl-17a-aza-D- homo-5α- androstane dimethoiodide
M.p.: 293° to 295°C (decomposition)
$[\alpha]_D^{25}$ = + 28.4° (c = 1 % of an aqueous solution)
NMR spectrum: 0.80 (19 CH_3) ; 1.48 (18 CH_3) ; 2.94 (17a CH_3) ; 3.12 (3α NCH_3)
Analysis for $C_{26}H_{48}N_2I_2$:
Calculated: C = 49.21 %, H = 7.57 %, N = 4.41 %;
Found: C = 49.00 %, H = 7.60 %, N = 4.30 %.

EXAMPLE 3

3α-(4-Methyl-piperazino)-17a-methyl-17a-aza-D-homo-5α-androstane diallylbromide

0.3 g (0.0007 moles) of 3α-(4-methyl-piperazino)-17a-methyl-17a-aza-D-homo-5α-androstane are dissolved in a mixture of 5 ml. of acetone and 2 ml. of methylene chloride, then 1.39 g. 0.0114 moles of allyl bromide are added to the solution. The reaction mixture is boiled for one hour, whereupon it is cooled to room temperature and diluted with 50 ml. of ether. The precipitated solid is filtered off and crystallized from a 1:5 mixture of ethanol and ether.

Yield: 0.40 g. (82.13 %) of 3α-(4-methyl-piperazino)-17a-methyl-17a-aza-D-homo-5α-androstane diallylbromide

M.p.: 200° to 202°C (decomposition)

$[\alpha]^{25}_D$ = + 3.6° (C = 1%) aqueous solution)

Analysis for $C_{31}H_{55}N_3Br_2$:

Calculated: C = 59.14 %, H = 8.74 %, N = 6.67 %, Br = 25.43 %;

Found: C = 58.91 %, H = 8.50 %, N = 6.41 %, Br = 25.1 %.

EXAMPLE 4

3β-Pyrrolidino-17a-methyl-17a-aza-D-homo-5α-androstane dimethobromide

The title compound is prepared starting from 3β-pyrrolidino-17a-methyl-17a-aza-D-homo-5α-androstane and methyl bromide, following the procedure described in Example 1.

Yield: 87 % of 3β-pyrrolidino-17a-methyl-17a-aza-D-homo-5α-androstane dimethobromide

M.p.: 270° to 280°C (decomposition)

$[\alpha]^{25}_D$ = 0° (c = 1 % in water)

NMR spectrum: 0.81 (19 CH_3) ; 1.48 (18 CH_3) ; 2.89 ; 2.95 (17a NCH_3) ; 3.11 (3β NCH_3)

Analysis for $C_{26}H_{48}N_2Br_2$:

Calculated: C = 56.93 %, H = 8.75 %, N = 5.10 %, Br = 29.19 %;

Found: C = 56.68 %, H = 8.50 %, N = 4.90 %, Br = 29.00 %.

3α-Mesyloxy-17-oxo-17a-aza-D-homo-5α-androstane

The title compound is prepared starting from 3α-hydroxy-17-oxo-17a-aza-D-homo-5α-androstane and methanesulphonic acid chloride, following the procedure described in Example 1a.

Yield: 87 % of 3α-mesyloxy-17-oxo-17a-aza-D-homo-5α-androstane

M.p.: 174° to 176°C

$[\alpha]^{25}_D$ = + 0.76° (c = 1 % in chloroform)

Analysis for $C_{20}H_{33}O_4NS$:

Calculated: C = 62.66 %, H = 8.61 %, N = 3.65 %;

Found: C = 62.40 %, H = 8.50 %, N = 3.45 %.

3β-Pyrrolidino-17-oxo-17a-aza-D-homo-5α-androstane

The title compound is prepared starting from 3α-Mesyloxy-17-oxo-17a-aza-D-homo-5α-androstane and pyrrolidine, following the procedure described in Example 1c.

Yield: 90 % of 3β-pyrrolidino-17-oxo-17a-aza-D-homo-5α-androstane

M.p.: 298° to 300°C

$[\alpha]^{25}_D$ = + 14.2° (c = 1 % in chloroform)

Analysis for $C_{23}H_{38}N_2$:

Calculated: C = 77.09 %, H = 10.61 %, N = 7.83 %;

Found: C = 77.00 %, H = 10.40 %, N = 7.60 %.

3β-Pyrrolidino-17a-aza-D-homo-5α-androstane

The title compound is prepared by reducing 3β-pyrrolidino-17-oxo-17a-aza-D-homo-5α-androstane with lithium-aluminium hydride, following the procedure described in Example 1d.

Yield: 87 % of 3β-pyrrolidino-17a-aza-D-homo-5α-androstane

M.p.: 208° to 210°C

$[\alpha]^{25}_D$ = 0.0° (c = 1 % in chloroform)

Analysis for $C_{23}H_{40}N_2$:

Calculated: C = 80.23 %, H = 11.62 %, N = 8.13 %;

Found: C = 79.92 %, H = 11.40 %, N = 8.00 %.

3β-Pyrrolidino-17a-methyl-17a-aza-D-homo-5α-androstane

The title compound is prepared starting from a mixture of 3β-pyrrolidino-17a-aza-D-homo-5α-androstane, formic acid and formaldehyde, following the procedure described in Example 1e.

Yield: 78] of 3β-pyrrolidino-17a-methyl-17a-aza-D-homo-5α-androstane

M.p.: 148° to 150°C

$[\alpha]^{25}_D$ = + 13.5° (c = 1 % in chloroform)

NMR spectrum: 0.75 (19 CH_3) ; 0.81 (18 CH_3) ; 2.20 (17a-NCH_3)
Analysis for $C_{24}H_{42}N_2$:
Calculated: C = 80.44 %, H = 11.50 %, N = 7.60 %;
Found: C = 80.19 %, H = 11.31 %, N = 7.36 %.

EXAMPLE 5

3β-Pyrrolidino-17a- methyl-17a-aza-D- homo-5α androstane dimethoidide

The title compound is prepared starting from 3β-pyrrolidino-17a- methyl-17a- aza-D-homo -5α- androstane and methyl iodide, following the procedure described in Example 2.

Yield: 88% of 3β-pyrrolidino-17a- methyl-17a-aza-D- homo-5α- androstane dimethoiodide
M.p.: 306° to 310°C (decomposition)
$[\alpha]_D^{25}$ = 0° (c = 1 % in water)
NMR spectrum: 0.81 (19 CH_3) ; 1.48 (18 CH_3) ; 2.88; 2.93 (17a-NCH_3) 3.10 (3β-NCH_3)
Analysis for $C_{26}H_{48}N_2I_2$:
Calculated: C = 49.21 %, H = 7.57 %, N = 4.41 %;
Found: C = 49.10 %, H = 7.31 %, N = 4.19 %.

EXAMPLE 6

3α- (4-Dimethyl-piperazino) -17a-dimethyl -17a-aza-D- homo-5α- androstane dibromide

2 g. (0.005 moles) of 3α- (4-methyl-piperazino) -17a- methyl-17a- aza-D-homo-5α- androstane are dissolved in a mixture of 25 ml. of acetone and 25 ml. of methylene chloride, then a solution of 2.85 g. (0.03 moles) of methyl bromide in 19 ml. of acetone is added. The reaction mixture is allowed to stand at room temperature for 24 hours, whereupon the precipitated crystals are filtered off and washed thoroughly with a 1:1 mixture of acetone and methylene chloride.

The product is dissolved in ethanol and the quaternary product is precipitated upon addition of ether.

Yield: 2.6 g. (87.2 %) of 3α- (4-dimethyl-piperazino) - 17a-dimethyl-17a- aza-D-homo -5α- androstane dibromide
M.p.: 284° to 286°C (decomposition)
$[\alpha]_D^{25}$ = + 2.2° (c = 1 % in water)
NMR spectrum: 0.78 (19 CH_3) ; 1.45 (18 CH_3) ; 2.93 (17a-NCH_3) ;
3.10 ; 3.15 (3α 4-dimethyl-piperazine)
Analysis for $C_{27}H_{51}N_3Br_2$:
Calculated: C = 56.15 %, H = 8.83 %, N = 7.27 %, Br = 27.27 %;
Found: C = 56.00 %, H = 8.60 %, N = 7.02 %, Br = 27.50 %.

3α- (4-Methyl-piperazino) -17a-methyl-17a-aza-D- homo-5α- androstane used as a starting compound is prepared as follows:–

3α-(4-methyl-piperazino) -17-oxo- 17a-aza-D- homo-5α- androstane

12 g. (0.31 moles) of 3β- mesyloxy-17-oxo -17a-aza-D-homo -5α-androstane are dissolved in 72 ml. of N-methylpiperazine. The solution obtained is refluxed for 22 hours then is cooled to room temperature. The precipitated crystalline product is filtered off, washed to N-methylpiperazine-free with water of 5°C and thereafter is dried at a temperature of 60° to 70°C until a steady weight.

The crystalline product is purified by boiling in acetonitrile.

Yield: 10.2 g. (84.1 %) of 3α- (4-methyl-piperazin) -17-oxo -17a- aza-D-homo -5α- androstane
M.p.: 268° to 270°C
$[\alpha]_D^{25}$ = +11.3° (c = 1 % in chloroform)
IR spectrum: 1680 cm^{-1} amide I
NMR spectrum: 0.80 (19 CH_3) ; 1.13 (18 CH_3) ; 2.27 (4-methyl-piperazine)
Analysis for $C_{24}H_{41}ON_3$:
Calculated: C = 74.41 %, H = 10.59 %, N = 10.85 %;
Found: C = 74.20 %, H = 10.36 %, N = 10.61 %.

3α- (4-methyl-piperazino) -17a-aza-D- homo-5α- androstane

7 g. (0.018 moles) of 3α-N- methylpiperazino-17- oxo-17a-aza-D-homo -5α- androstane are dissolved in 140 ml. of dry dioxane, then 7 g. of lithium-aluminium hydride are added to the solution, under a nitrogen flow and vigorous stirring. The reaction mixture is boiled in a flask equipped with a reflux condenser supplied with a $CaCl_2$-tube, under a nitrogen flow for 32 hours. The reaction mixture is then cooled to 10°C, whereupon the excess of lithium-aluminium hydride is decomposed with 15 ml. of water, under vigorous stirring and intensive nitrogen flow.

The precipitate, which consists of lithium hydroxide and aluminium hydroxide is filtered off and washed several times with dioxane. The dioxane solution is evaporated to dryness and the residue is crystallized from acetonitrile.

Yield: 6.0 g. (89.0 %) of 3α- (4-methyl-piperazino) -17a-aza-D- homo-5α- androstane

M.p.: 119° to 120°C
$[\alpha]_D^{25}$ = + 2.6° (c = 1 % in chloroform)
NMR spectrum: 0.80 (19 CH_3) ; 1.03 (18 CH_3) ; 2.27 (4-methyl-piperazine) ; 2.80 (17-CH_2)
Analysis for $C_{24}H_{43}N_3$:
Calculated: C = 77.21 %, H = 11.52 %, N = 11.26 %;
Found: C = 77.00 %, H = 11.31 %, N = 11.02 %.

3α-(4-methyl-piperazino)-17a-methyl-17a-aza-D-homo-5α-androstane

4.1 g. (0.010 moles) of 3α-N-methyl-piperazino-17a-aza-D-homo-5α-androstane are dissolved in a mixture of 48 ml. of formic acid and 37 ml. of formaldehyde and the reaction mixture is refluxed for 2.5 hours. Thereafter a further 37-ml. portion of formaldehyde is added to the reaction mixture and boiling is continued for further two hours. The reaction mixture is then evaporated to nearly dryness and the pH-value is adjusted to 10 with a 5 % aqueous sodium hydroxide solution. The precipitated amorphous product is filtered off, washed to neutral with water and dried at a temperature of 50° to 60°C *in vacuo*. The product is crystallized from ether.

Yield: 3.3 g. (77.64 %) of 3α-(4-methyl-piperazino)-17a-methyl-17a-aza-D-homo-5α-androstane
M.p.: 152° to 155°C
$[\alpha]_D^{25}$ = + 16.5° (c = 1 % in chloroform)
NMR spectrum: 0.77 (19 CH_3) ; 0.82 (18 CH_3) ; 2.18 (17a-NCH_3) ; 2.26 (4-methylpiperazine)
Analysis for $C_{25}H_{45}N_3$:
Calculated: C = 77.51 %, H = 11.62 %, N = 10.85 %;
Found: C = 77.30 %, H = 11.40 %, N = 10.60 %.

EXAMPLE 7

3α-Pyperidino-17a-methyl-17a-aza-D-homo-5α-androstane dimethoiodide

The title compound is prepared starting from 3α-piperidino-17a-methyl-17a-aza-D-homo-5α-androstane and methyl iodide, following the procedure described in Example 2.

Yield: 85 % of 3α-pyperidino-17a-methyl-17a-aza-D-homo-5α-androstane dimethoiodide
M.p.: 274° to 276°C
$[\alpha]_D^{25}$ = + 32.2° (C = 1 % in water)
Analysis for $C_{27}H_{50}N_2I_2$:
Calculated: C = 49.39 %, H = 7.62 %, N = 4.26 %, I = 38.70 %;
Found: C = 49.10 %, H = 7.41 %, N = 4.00 %, I = 38.40 %.

3α-Pyperidino-17-oxo-17a-aza-D-homo-5α-androstane

The title compound is prepared starting from 3β-mesyloxy-17-oxo-17a-aza-D-homo-5α-androstane and piperidine, following the procedure described in Example 1/c.

Yield: 90 % of 3α-pyperidino-17-oxo-17a-aza-D-homo-5α-androstane
M.p.: 270° to 272°C
$[\alpha]_D^{25}$ = + 13.7° (c = 1 % in chloroform)
IR spectrum: 1675 cm^{-1} amide I
Analysis for $C_{24}H_{40}N_2O$:
Calculated: C = 77.41 %, H = 10.75 %, N = 7.52 %;
Found: C = 77.19 %, H = 10.50 %, N = 7.31 %.

3α-Pyperidino-17a-aza-D-homo-5α-androstane

The title compound is obtained starting from 3α-piperidino-17-oxo-17a-aza-D-homo-5α-androstane by reduction with lithium-aluminium hydride, following the procedure described in Example 1d.

Yield: 81 % of 3α-pyperidino-17a-aza-D-homo-5α-androstane
M.p.: 108° to 110°C
$[\alpha]_D^{25}$ = + 7.6° (c = 1 % in chloroform)
Analysis for $C_{24}H_{42}N_2$:
Calculated: C = 78.21 %, H = 11.73 %, N = 7.60 %;
Found: C = 78.03 %, H = 11.54 %, N = 7.79 %

3α-Pyperidino-17a-methyl-17a-aza-D-homo-5α-androstane

The title compound is prepared starting from 3α-piperidino-17a-aza-D-homo-5α-androstane by alkylation with a mixture of formic acid and formaldehyde, following the procedure described in Example 1e.

Yield: 85 % of 3α-pyperidino-17a-methyl-17a-aza-D-homo-5α-androstane
M.p.: 176° to 177°C
$[\alpha]_D^{25}$ = + 17.8° (c = 1 % in chloroform)
Analysis for $C_{25}H_{44}N_2$:
Calculated: C = 80.64 %, H = 11.82 %, N = 7.52 %;
Found: C = 80.73 %, H = 11.58 %, N = 7.72 %.

EXAMPLE 8

3α-Pyrrolidino -17a- methyl -17a- aza -D-homo-5α- androstane diethanesulphonate

2 g. of 3α-pyrrolidino -17a- methyl -17a- aza -D-homo-5α- androstane are dissolved in 30 ml. of dry ethanol, then 1.2 g. of ethanesulphonic acid are added to the solution. Thereafter 2/3 of the ethanol is distilled off, then 50 ml. of ether are added to the residue. The precipitated white crystalline substance is filtered off, thoroughly washed with several portions of ether and is dried over phosphorous pentoxide *in vacuo*.

Yield: 3.0 g. (93.7 %) of 3α-pyrrolidino -17a- methyl -17a- aza -D-homo-5α- androstane diethanesulphonate
M.p.: 268° to 270°C (decomposition)
$[\alpha]_D^{25} = +62°$ (c = 1 % in water)
Analysis for $C_{28}H_{54}S_2N_2O_6 . H_2O$:
Calculated: C = 58.13 %, H = 9.34 %, N = 4.84 %;
Found: C = 57.92 %, H = 9.10 %, N = 4.62 %.

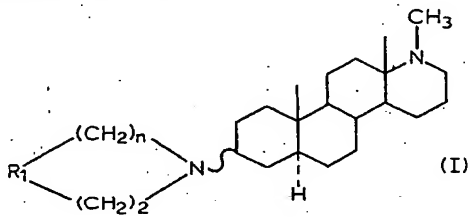
EXAMPLE 9

Injection solution

10 g. of 3α-pyrrolidino -17a- methyl -17a- aza -D- homo-5α- androstane dimethobromide are dissolved in 2000 ml. of pyrogene-free physiological sodium chloride solution and thereafter the solution obtained is filled into ampoulles. Into a 2-ml. brown ampoulle 1 ml. of the above injection solution is filled. The ampoulles are sterilized in a known manner.

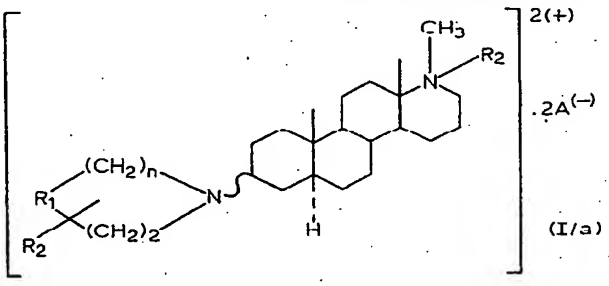
CLAIMS

1. Compounds of general formula I



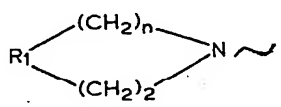
(I)

wherein
R_1 represents a methylene or $\geq N-CH_3$ group;
n is 1 or 2; and
the symbol ~ indicates an α- or β- configuration
and the acid addition salts thereof and the quaternary salts of general formula Ia



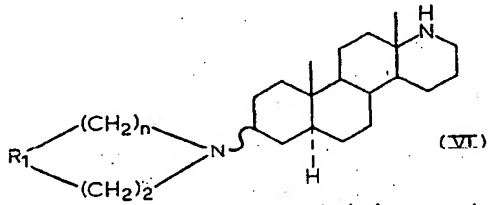
(I/a)

wherein R_1, n and ~ are as defined above, R_2 represents an alkyl or alkenyl group containing from 1 to 4 carbon atoms and A represents a halogen atom with the proviso that, when R_1 represents an $N-CH_3$ group then the R_2 group attached to the ring including R_1 is attached to the nitrogen atom of said R_1 group and when R_1 represents a methylene group then the R_2 group attached to the ring including R_1 is attached to the nitrogen atom of the group



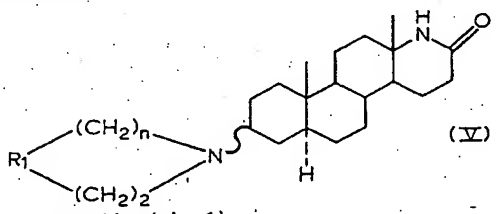
2. Quaternary salts of general formula Ia as defined in claim 1.
3. Physiologically compatible acid addition salts of compounds of general formula I as defined in claim 1.
4. 3-α-Pyrrolidino -17a- methyl -17a- aza -D-homo -5α- androstane dimethoiodide.

5. 3β-Pyrrolidino -17a- methyl -17a- aza -D-homo-5α- androstane dimethoiodide.
6. 3α-Pyrrolidino -17a- methyl -17a- aza-D-homo -5α- androstane dimethobromide.
7. 3β-Pyrrolidino -17a- methyl -17a- aza-D- homo-5α- androstane dimethobromide.
8. Compounds as claimed in claim 1, other than those claimed in any of claims 5 to 7, as herein specifically disclosed in any of Examples 1 to 8.
9. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises treating a compound of formula VI,



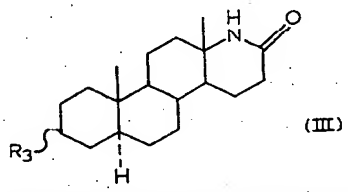
(VI)

(wherein R_1, n and ~ are as defined in claim 1) with a methylating agent.
10. A process as claimed in claim 9 wherein the methylating agent is a mixture of formic acid and formaldehyde.
11. A process as claimed in claim 9 or claim 10 wherein the compound of formula VI is obtained by reducing a compound of formula V,



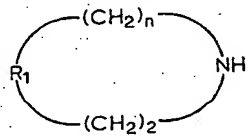
(V)

(wherein R_1, n and ~ are as defined in claim 1).
12. A process as claimed in claim 11 wherein reduction is effected by means of a complex metal hydride.
13. A process as claimed in claim 12 wherein the complex metal hydride is lithuim aluminium hydride or sodium-bis 2 methoxy-ethoxy - lithium aluminium hydride.
14. A process as claimed in any of claims 11 to 13 wherein the compound of formula V is obtained by reacting a compound of formula III,



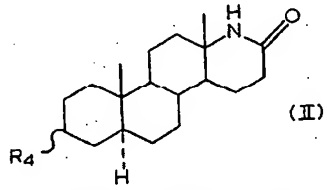
(III)

(wherein R_3 represents an alkane-, aryl- or aralkane- sulphonyloxy group) with a compound of formula IV



(IV)

(wherein R_1 and n are as defined in claim 1)
15. A process as claimed in claim 14 wherein the compound of formula III is obtained by reacting a compound of formula II,



(II)

(wherein R_4 represents a hydroxyl group) with an alkane-, aryl- or aralkane-sulphonic acid halide
16. A process as claimed in claim 15 wherein the compound of formula II is reacted with methane-sulphonic acid chloride or *p*-toluene-sulphonic acid chloride.
17. A process as claimed in claim 15 or claim 16 wherein the reaction of the compound of formula II with the sulphonic acid halide is effected in the presence of a tertiary amine.
18. A process as claimed in claim 17 wherein the tertiary amine is pyridine.

19. A process as claimed in claim 17 or claim 18 wherein the reaction of the compound of formula II with the sulphonic acid halide is effected in the presence of an inert solvent.

20. A process as claimed in claim 19 wherein the inert solvent is dichloromethane.

21. A process for the preparation of acid addition salts of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula I as defined in claim 1 with an acid.

22. A process for the preparation of acid addition salts of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula I as defined in claim 1 with an acid.

22. A process for the preparation of quaternary salts of general formula Ia as defined in claim 1 which comprises reacting a compound of formula I as defined in claim 1 with a compound of formula R_2A (wherein R_2 and A are as defined in claim 1)

23. A process as claimed in claim 22 wherein the compound of formula I is reacted with methyl bromide, methyl iodide or allyl bromide.

24. A process for the preparation of compounds as claimed in claim 1 substantially as herein described.

25. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any of Examples 1 to 8.

26. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any of claims 9 to 25.

27. Pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I as defined in claim 1 or a physiologically compatible acid addition salt thereof or a quaternary salt of formula Ia as defined in claim 1, in association with a pharmaceutical carrier or excipient.

28. Compositions as claimed in claim 27 in a form suitable for parenteral administration.

29. Compositions as claimed in claim 27 or claim 28 in the form of dosage units.

30. Pharmaceutical compositions as claimed in claim 27 substantially as herein described.

31. Pharmaceutical compositions substantially as herein described in Example 9.

32. Compounds of general formula VI as defined in claim 9.

33. A process for the preparation of compounds of general formula VI as defined in claim 9 substantially as herein described.

34. Compounds of general formula V as defined in claim 11.

35. A process for the preparation of compounds of general formula V as defined in claim 11 substantially as herein described.

36. Compounds of general formula III as defined in claim 14.

37. A process for the preparation of compounds of general formula III as defined in claim 14 substantially as herein described.

38. Each and every novel method, process, compound and composition herein disclosed.

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